# THE USE OF RECOMBINANT ACTIVATED FVII (rFVIIa, NOVOSEVEN®) IN THE TREATMENT OF PATIENTS WITH HAEMOPHILIA AND INHIBITORS

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## INTRODUCTION

The development of inhibitors to factor VIII (FVIII) has become one of the most serious complications in the treatment of haemophilia patients, occurring in 15-30% of haemophilia A (HA) patients and 1-3% of haemophilia B (HB) patients. (1)
The management of acute bleeding episodes may use different approaches: human factor VIII or factor IX (2), porcine factor VIII (3), prothrombin complex concentrates (PCC), activated prothrombin complex concentrates (aPCC) (4-6) and more recently recombinant activated factor VII (rFVIIa, Novoseven) (7).
rVIIa is a potent by-passing agent which mechanism of action is most probably to provide a full thrombin burst, in the absence of FVIII/FIX, on the activated platelets and represents a major therapeutic advance in the treatment of haemophilia patients with high-titter inhibitor (8). Its safety and efficacy in the treatment of haemophiliacs with inhibitors to FVIII or IX has been investigated in clinical studies since 1989 (9).
RFVIIa has been used in our country for the first time, in Compassionate Use Program, in November 1994. Since 1996 foi comercializado em Portugal e utilizado no tratamento dos doentes com hemofilia e inibidores.
The aim of this study is to evaluate, retrospectively, the efficacy and safety of rFVIIa in the treatment of acute bleeding episodes and prophylactic, in surgical procedures, in the period between Nov.1994-Dec1999, in the patients followed in Hospital S. José and Hospital de Santa Maria in Lisbon.

## PATIENTS AND METHODS

The patient population consisted of 15 patients, 14 had hemophilia A (13 severe, 1 mild) and 1 had severe hemophilia B; mean age 25,7 years (range: 4-50), mean weight 56.4 Kg (range :22-100).
RFVIIa was used in the treatment of 90 acute bleeding episodes. (Table 1)
2 patients have been treated on a compassionate use basis, in two lifethreatening bleeding episodes.
In the treatment of acute hemarthroses rFVIIa was administered by intravenous bolus injection in the dose range 80-90mcg/Kg. The initial dose was given every 2 h, in a total of 3 injections or until clinical improvement was observed.
O tratamento dos hematomas intramusculares, (including psoas-iliac hematomas), dos hematomas retroperitoneais e do subdural hematoma foi efectuado com rFIIa em Bolus Intermitent Injections (BII), na dosagem de 80-100mcg/Kg, de 2/2 h nas primeira 24 horas, com alargamento dos intervalos para 3/3, 4/4 e 6/6 horas, de acordo com a sintomatologia clínica e os exames de controlo.
Quando usado em profilaxia em casos de cirurgia urgente o procedimento foi idêntico, variando o nº de dias de tratamento.
The efficacy was assessed as: an excellent/effective (E) response was defined when the bleeding ceased or decreased substantially, or when there was a significant relief of pain and swelling within 8-12 hours; a partially effective (PE) response was defined as some relief of symptoms, or an improvement of mobility but the bleeding continued; no clinical improvement or if bleeding remained or worsened, there was an ineffective response (IR).
Epsilon aminocaproic acid, 100 mg/Kg, every 6 h, foi utilizado como terapêutica adjuvante, nos casos de cirurgia, hemorragias das mucosas e na extracção dentária.
Laboratory monitoring included platelet count, estimations of prothrombin time (PT/INR) and levels of factor VII:C. Both FVII:C and PT/INR were performed by a one-stage assay, using a rabbit brain thromboplastin.

## RESULTS

### EFFICACY

*Joint bleeds (Fig.1)*: an excellent/effective response to treatment was observed in 48 (79%) episodes. In 8 (13%) episodes the response was evaluated as partially effective and in 5 (8%) ineffective.
Mean treatment/episode: 3,2 (range:1-9).
Partially effective and ineffective responses are related to target joints (knee, elbow) assim como o maior nº de tratamentos por episódio. In one patient (pte. 15) in home treatment, all the joint bleeds were evaluated as effective, and the mean treatment per episode was 2,6 (range: 1-6).
*Muscle bleeds (Fig 1)*: In this group of 11 episodes we included one ilio-psoas haematoma and 10 other intramuscular haematomas (thigh, calf, lombar, neck).
The response to treatment was evaluated as excellent/effective in 9 (82%) episodes, partially effective in one case (4%) and ineffective in one case (4%). Mean treatment/episode - 15,5 (range:3-45).

| Case nº | Hem. type | Age | Type of bleed |
|---|---|---|---|
| 1 | A | 23 | Subdural haematoma* (1) |
| 2 | A | 40 | Post-nefrectomy abdom.haematoma(1) |
| 3 | A | 15 | Joint bleed (3) Muscle bleed(2)<br>Respiratory tract bleed (1)<br>Prophylatic of lumbar puncture (1) |
| 4 | A | 23 | Oral cavity bleed (1)<br>Nose bleed (1) |
| 5 | A | 18 | Joint bleed (3) Muscle bleed (4)<br>Retroperitoneal hemorrhage (2)<br>Dental bleed (2) Tongue bleed (1) |
| 6 | A | 14 | Joint bleed (5)<br>Gastrointestinal bleed (1) |
| 7 | A | 29 | Joint bleed (17)<br>Gastrointestinal bleed (1) |
| 8 | A | 41 | Circumcision (1)<br>Joint bleed (2) |
| 9 | A | 35 | Neck Muscle bleed (1) |
| 10 | A | 50 | Muscle bleed (3) |
| 11 | A | 31 | Retroperitoneal hemorrhage (1) |
| 12 | A | 29 | Joint bleed (3)<br>Muscle bleed (1) |
| 13 | A | 6 | Radioactive synoviorthesis (2)<br>Central catheter removal (1)<br>Joint bleed (9) |
| 14 | B | 4 | Subdural haematoma/craniotomy* (1) |
| 15 | A | 27 | Joint bleed (19) |

Table 1 – Characteristics of the patients given rFVIIa and bleeding episodes.

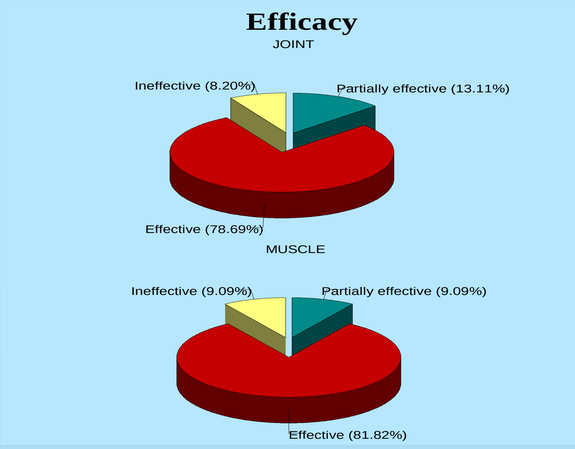


Figure 1- Joint and muscle bleeds treatment efficacy.

*Prophylactic (Table 2)* - rFVIIa proved to be very effective in five (83%) episodes, with an excellent recovery of the child (pte. 14) with the subdural haematoma, with complete recovery of the neurological symptoms. In one case (pte.5) satisfactory haemostasis was not achieved, for dental extraction, with subsequent oozing, probabilly because of suboptimal rFVIIa and/or antifibrinolytic therapy (Table 2).

| PROPHYLATIC | | Doses/treat. | Efficacy |
|---|---|---|---|
| Surgery | Craniotomy for subdural hematoma | 100 | E |
| | Post-nefrectomy abdominal hematoma | 114 | E |
| Other Procedures | Lumbar puncture | 14 | E |
| | Dental extraction | 13 | PE |
| | Central Catheter removal | 31 | E |
| | Bilateral Synoviortesis | 31 | E |

Table 2 – Novoseven use in prophylaxis, number of doses per episode and efficacy

*Retroperitoneal hematomas* – an excellent response was observed in all cases, with evident relief of pain, less than 24 hours after the beginning of the treatment.
*Other haemorrhages (Table 3)* - an excellent/effective response was observed in 7 episodes (87,5%) and a partially effective response in the case of the tongue haemorrhage. The patient had a dental spicule that caused trauma and after dental correction the haemorrhage stopped.
Mean treatment/episode: 13,4 (range: 2-36).

| Other hemorrhages | Doses/treat. | Efficacy |
|---|---|---|
| Post-circumcision | 8 | E |
| Gastrointestinal | 5-6 | E |
| Oral cavity | 2-20 | E |
| Tongue | 27 | PE |
| Nasal | 36 | E |
| Respiratory tract | 3 | E |

Table 3- Novoseven use in other hemorrhages, number of treatments per episode and efficacy.

ADVERSE EVENTS- A total of 4 non-serious adverse events were recorded: local thrombophlebitis (3 cases) and fever and cutaneous erythema (1 case).

LABORATORY MONITORING- Although the therapeutic level of rFVII:C is not yet well established, our target was to maintain plasma FVII:C level above 10U/mL. The levels of post-infusion FVII:C had been determined in 5 cases. The highest FVII:C level recorded in each individual range from 8,7 to 23,4U/mL. These differences may be related to differences in individual recovery of rFVIIa.


## RESULTS AND CONCLUSIONS

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